II. Remarks

A. Status of the Claims

Claims 26 and 27 are currently pending. Claims 1-14, 16-19 and 24 were previously cancelled. Claims 15, 20-23, 25 and 28-29 have been cancelled without prejudice. Applicants respectfully submit that no new matter has been added by virtue of this amendment.

B. Claim Rejections Under 35 U.S.C. § 103(a) over Malterud et al., Manthey et al. and Bok et al.

In the Office Action, the Examiner maintained the rejection of claims 15, 20-23 and 25-26 under 35 U.S.C. § 103(a) as being unpatentable over Malterud et al. ("Inhibitors of 15-lipoxygenase from orange peel", *J. Agric. Food Chem* (2000 Nov); 48(11): 5576-80, Abstract) and U.S. Patent No. 6,184,246 to Manthey et al. in view of U.S. Patent No. 6,096,364 to Bok et al.

Applicants note that all of the rejected claims have been cancelled without prejudice except for claims 26 and 27 which are directed to methods of treating abnormalities resulting from insulin resistance with a polymethoxyflavone composition consisting of nobiletin and tangeretin.

With respect to present claims 26 and 27, the Examiner stated that "in a majority of formulations of polymethoxyflavones, the presence of nobiletin and tangeretin is so common and does not seem to ever be absent when mentioned with other polymethoxyflavones. Thus, one may conclude that a formulation void of any other polymethoxyflavone besides nobiletin and tangeretin may be deficient in the way of addressing the limitation drawn to an effective ratio to reduce levels by at least 26%."

Applicants respectfully disagree with the Examiner's conclusion, and submit that the Examiner is not considering that as demonstrated in the present application, certain polymethoxyflavones may be more potent than others. For example, the Examiner's attention is drawn to Figure 11 of the present specification, which depicts a graph of the in-vitro inhibition of alpha-glucosidase by citrus flavonoids and coumarins. As depicted in the graph, out of the 5 citrus flavonoids tested, nobiletin had the highest inhibition of alpha-glucosidase, and tangeretin has the third highest inhibition. It should also be noted

that from at approximately 80 μg/ml to 200 μg/ml, tangeretin had the second highest inhibition of alpha-glucosidase. Accordingly, Applicants submit that Figure 11 evidences that individual polymethoxyflavones have varying potencies. Thus, contrary to the Examiner's position, Applicants submit that in view of the present specification, one of skill in the art would not conclude that nobiletin and tangeretin may be deficient in the way of addressing the limitation drawn to reducing levels [of serum insulin] by at least 26%.

Upon review of the office action, claims 26 and 27 did not appear to have been discussed in the rejections over the prior art. However in the order of completeness, Applicants submit that, in view the Malterud and Manthey references in view of the Bok reference, one of skill in the art would not be motivated to administer a composition with a polymethoxyflavone composition consisting of nobiletin and tangeretin to treat abnormalities resulting from insulin resistance, as recited in present claims 26 and 27.

The Manthey reference fails to teach or suggest the administration of polymethoxyflavones for anything other than the inhibition of the production of cytokines; the Malterud reference recites a list of virtually every element found in orange peel, i.e., hexamethoxyflavone, sinensetin, nobiletin, tangeretin, tetramethylscutellarin, heptamethoxyflavone, hesperidin and ferulic acid; and the Bok reference only teaches a method of lowering blood glucose levels in diabetic patient by administration of bioflavonoids which are not polymethoxyflavones. Therefore, Applicants submit that, in view of the cited references, one of skill in the art would not be motivated to use an effective amount of the two specifically claimed polymethoxyflavones to reduce serum insulin levels by 26% as recited in claims 26 and 27.

Further, Applicants respectfully point out that in their previous responses, the position was asserted that the Malterud, Manthey and Bok references are improperly combinable, as the Malterud reference is directed to a different field of endeavor than the Manthey and Bok references. Namely, the Manthey reference is directed to "a method of inhibiting the production of cytokines" which associated diseases include "septic shock, cancer, cachexia, chronic rheumatism, ulcerative colitis, Crohn's disease...". Manthey et al. at Abstract and Col. 2, lines 58-59, whereas the Malterud and Bok references are directed to inhibition of 15-lipoxygenase and glucose reduction, respectively. The

Examiner had rebutted this position by citing the Natarajan reference to support the combinability of the references. In response, Applicants submitted arguments as to why the Natarajan reference did not evidence what was known in the art at the time of filing of the present application, and the Examiner subsequently withdrew the Natarajan reference in the current Office Action. However, the Examiner continues to cite the combination of the Malterud, Manthey and Bok references, without addressing Applicants' position that the references are improperly combinable.

Accordingly, Applicants reassert that the Manthey, Malterud and Bok references are improperly combinable, as discussed above and as discussed in Applicants' previous responses. Therefore, Applicants submit that one of skill in the art would not combine the Manthey reference with the Malterud and Bok references, as they are directed to different fields of endeavor.

Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) over the Malterud and Manthey references in view of the Bok reference be removed.

C. Claim Rejection Under 35 U.S.C. § 103(a) over Malterud et al., Manthey et al. and Bok et al. further in view of Pershadsingh and Robbins

In the Office Action, the Examiner rejected maintained the rejection of claim 25 under 35 U.S.C. § 103(a) as being unpatentable over the Malterud, Manthey and Bok references as applied to claims 15 and 20-23, further in view of U.S. Patent No. 6,087,385 to Pershadsingh et al. and U.S. Patent No. 3,867,541 to Robbins.

Applicants note that claim 25 has been cancelled without prejudice, making this rejection moot.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over the Malterud, Manthey and Bok references in view of the Pershadsingh and Robbins references be removed.

III. Conclusion

In view of the amendments made and arguments presented, it is believed that all claims are in condition for allowance. If the Examiner believes that issues may be

resolved by a telephone interview, the Examiner is invited to telephone the undersigned at (973)597-2404. The undersigned also may be contacted via e-mail at rparadiso@lowenstein.com. All correspondence should be directed to our address listed below.

AUTHORIZATION

The Commissioner is hereby authorized to charge any fees that may be required, or credit any overpayment, to Deposit Account No. 50-1358.

Respectfully submitted,
Lowenstein Sandler PC

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